Molecular Modeling as a Tool for Understanding Human Health Risks

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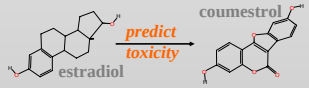
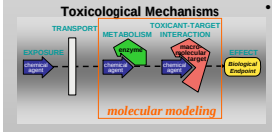
Why Molecular Modeling for Evaluating Chemical Toxicity?

Computational methods such as molecular modeling can be used as tools in order to evaluate the potential health and environmental effects of chemicals, particularly when all of the relevant information is not available prior to the risk assessment.

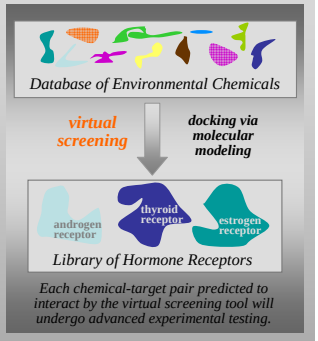
- Predictions of a potential toxicological effect of an environmental chemical based on knowledge of the effects of "similar" chemicals





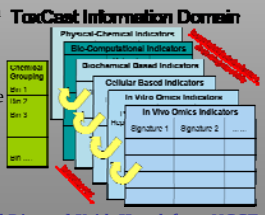
- Aids in the understanding of toxicological mechanisms, which can be incorporated into the risk assessment

- Application of virtual screening tools based on molecular modeling as a means of categorizing and prioritizing chemicals for experimental testing



- The availability of atomic-level details of the interactions between environmental chemicals and molecules in the body, such as proteins or DNA

- Integration into ***ToxCast***, a multi-level information domain scheme for studying chemical toxicity.
  - *First phase:* Perform a comprehensive study on a set of diverse chemicals across all information domains.
  - *Second phase:* The information that is gathered will be used to extract relationships among the information domains.
  - *Third phase:* Utilize these relationships to inform computer models in order to improve their abilities to suggest priorities for future bioassays and other regulatory purposes.



This work is a collaboration with Bob Kavlock, David Dix, and Keith Houck from NCCT

Molecular modeling tools have been developed primarily for the design of pharmaceuticals. A significant difference between prioritizing toxicity testing and enriching a pharmaceutical database is the relative importance of *false negatives*, which are toxic chemicals that are erroneously categorized as non-toxic. In environmental screens, a false negative may dangerously eliminate a chemical from further testing while in pharmaceutical discovery, the existence of false negatives is much less significant if true positives remain.

Molecular Modeling Methods for Predicting Chemical Toxicity

Methods that Estimate Binding of Toxicants to Targets

Molecular Descriptors, QSARs

Docking into *Rigid* Macromolecular Targets

Docking into *Flexible* Macromolecular Targets

Mixture of Quantum Mechanics and Molecular Mechanics (QM/MM)

Free Energy Perturbation

Throughput

Quality

Rigid Docking: Geometry of the macromolecular target is rigid while a "best fit" is calculated for a variety of orientations and geometrical conformations of the chemical agents.

Fast computational screening tool, but accuracy is not ideal

Flexible Docking: Similar to rigid docking, except that a portion of the geometry of the macromolecular target is flexible so that the binding region can contort to properly fit chemical agents.

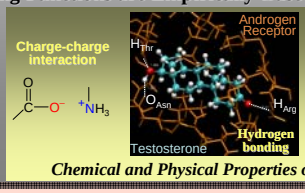
Computationally intensive, but accuracy is more reliable.

Docking Scoring Functions are Empirically-Based

Docking Scoring = Function

Shape Fitting

+



Chemical and Physical Properties of Interaction

Results

Endocrine Disrupting Compounds (EDCs). The function of nuclear receptors such as the estrogen receptor (ER) is to regulate diverse functions, including reproduction, development, and metabolism. A common mechanism for EDCs is to mimic or inhibit the binding of hormone molecules to these nuclear receptors, which disrupts their normal biological function and can lead to adverse health effects, including cancer. Many natural and synthetic environmental chemicals are suspected to be EDCs.

Flexible docking studies with ERα (right) was used to screen a set of chemicals that represent a wide range of biological activity. *This work is a collaboration with Susan Laws from NHEERL*

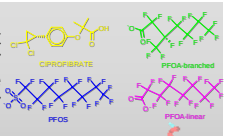
The lack of separation in the docking calculations (right) between chemical agents that do not bind or bind weakly to ERα is an artifact of using tools that are designed for pharmaceuticals.

Docking scoring functions need to be optimized for chemical toxicity by focusing on minimizing the false negative rate.

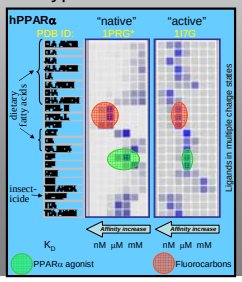
	Docking Energy
[R] EM652	-56.0
[S] EM652	-60.2
diethylstilbestrol	-40.5
mesa-hexestrol	-41.5
RS-hexestrol	-44.5
SS-hexestrol	-42.3
4-hydroxytamoxifen	-60.9
17b-estradiol (natural ligand)	-43.8
coumestrol	-44.5
(R,R)-5,11-cis-diethyl-5,6,11,12-tetrahydrochrysene-2,8-diol	-41.2
phenol, 4-heptyl	-30.9
morin	-49.5
diadzein	-44.3
ethyl-4-hydroxybenzoate	-31.7
phenol, 4-chloro-3-methyl	-24.0
[S] 2-phenyl, 1-propanol	-24.5
[R] 2-phenyl, 1-propanol	-23.6
1,4-dihydroxy-2-naphthoic acid	-32.9
5-chloro-2-(2,4-dichlorophenoxyl)phenol	-39.0

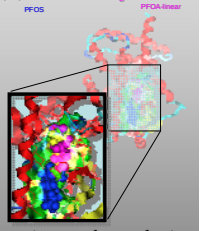
increasing experimental binding affinity

Perfluorinated compounds, such as PFOA and PFOS, are persistent environmental pollutants that are implicated with binding to the nuclear receptor PPARα, which could result in potential endocrine disrupting properties. PPARs are a family of nuclear receptors that function as transcription factors and regulate multiple metabolic processes. PPARα is found primarily in the liver and muscle and is linked to fatty acid oxidation and diabetes type II.



Rigid docking studies with **PPARα (figure to the right) suggest about 10-100 times increased affinity of the fluorocarbon class relative to the agonist class for the simulated "native" PPARα structure, and a similar order of magnitude as the agonist, CIP, for the active-bound conformation.**



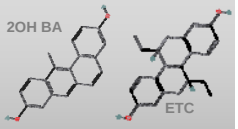


The picture above depicts the binding pocket of PPARα with and overlay of the lowest energy pose for each of the circled hits (figure to the left).

Polycyclic Aromatic Hydrocarbons (PAHs) are combustion byproducts that are ubiquitous environmental chemicals. Some PAHs are potent animal carcinogens and some PAHs have also been shown to have endocrine disruption activity.

Rigid docking studies with several alpha estrogen receptors (ERα) of the native ligands (top) and PAH metabolites

	ER-1L2I [ETC]	ER-1GWR [E2]	ER-3ERD [DES]	ER-3ERT [OHT]
Diethyl, tetrahydro-chrysene diol (ETC), x-ray	**-11.2**	-9.2	-8.2	-6.9
Estradiol (E2), x-ray	-8.7	**-11.0**	-8.2	-4.7
Diethyl stilbestrol (DES), x-ray	-8.8	-8.0	**-9.6**	-9.1
Tamoxifen (OHT), x-ray	***	***	***	**-10.9**
3,9-dihydroxy benzanthracene (2OH BA)	**-10.1**	-9.1	-9.6	-8.0
3,9-dihydroxy 12-methyl BA	**-10.0**	-8.6	-8.5	-8.4
2OH (-)-anti-BaPDE	**-10.0**	-7.6	-7.2	-4.8
3OH (-)-BaPD equatorial diol	**-9.8**	-8.7	-8.8	-6.1
3,9-dihydroxy 12-methyl BA enantiomer	**-9.8**	-9.5	-8.9	-7.3
2OH (+)-anti-BaPDE	**-9.6**	-7.6	-6.3	-7.6
3OH (+)-BaP equatorial diol	**-9.4**	-8.1	-8.5	-6.7
(-)-anti-BaPDE	**-9.3**	-7.9	-6.4	-4.8
3,9-dihydroxy 7-methyl BA	**-9.1**	-7.4	-9.0	-5.2
(+)-syn-BcPhDE	**-8.9**	-7.9	-5.9	-6.0
(+)-anti-BaPDE	**-8.8**	-7.5	-6.0	-5.5
3OH (-)-BaPD axial diol	**-8.6**	-7.5	-7.4	-4.0
(-)-syn-BcPhDE	-8.3	**-8.6**	-6.6	-5.9
average PAH Docking Score	-9.4	-8.2	-7.6	-6.2



The PAHs bind best to ER-1L2I, the ER structure that was crystallized with an ER agonist, tetrahydrochrysene diol (ETC). ETC has a chemical structure similar to PAHs (above).

The ER antagonist, tamoxifen (OHT), does not bind to the other three ER crystal structures (indicated by ***) due to its large size and the use of rigid docking methods.

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